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(54) Title: ADDITIVES FOR BIOERODIBLE POLYMERS TO REGULATE DEGRADATION
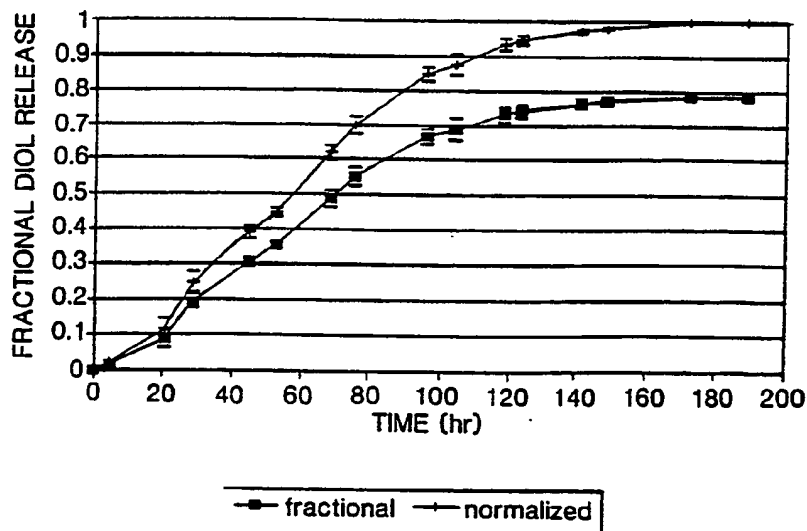
(57) Abstract

The degradation rates of bioerodible polymers used in sustained-release drug delivery formulations are regulated by the in-
corporation in the polymer of a regulating agent, or erosion rate modifier, which has substantially higher solubility in the polymer
than in water. In polymers whose degradation rate is accelerated or decelerated by acids, bases or both, the erosion rate modifier
is an acid or base with the appropriate solubility characteristics. Dissolving of an acid or base erosion rate modifier in the polym-
er as a solid solution permits the use of an acid or base of weaker strength than those used as erosion rate modifiers in the prior
art, and achieves a more prolonged regulating effect on the polymer with a lesser potential for undesired injury to the polymer, to
the drug, or to the tissues or the organism to which the formulation is applied.

ADDITIVES FOR BIOERODIBLE POLYMERS
TO REGULATE DEGRADATION

This invention resides in the field of bioerodible
polymers for use as drug delivery vehicles. In particular, this
5 invention addresses means for controlling the rate of biodegradation
and degradation in general of such polymers.

BACKGROUND OF THE INVENTION

One of many known methods of achieving sustained delivery
of a drug is by incorporating the drug in a solid polymeric matrix
10 formed from a bioerodible polymer. Formulations of this type are
primarily used for parenteral administration. The matrix may assume
a variety of forms, but most often is either in the shape of thin
rods suitable for injection, or microscopic particles suitable for
application as a dry sprinkle or in a suitable liquid vehicle for
15 injection.

The term "bioerodible" refers to the quality of the
polymer that causes it to be degraded or eroded *in vivo*. This occurs
either through enzymatic action or other types of action, and
decomposes the polymer into biocompatible, non-toxic by-products
20 which are further metabolized or excreted from the body through the
normal physiological pathways, without raising an immunological
reaction.

Among the wide variety of polymers having this quality,
some which are of particular interest in this invention are
25 poly(orthoester)s and poly(orthocarbonate)s. Such bioerodible
polymers are disclosed in Schmitt, U.S. Patent No. 4,070,347,
January 24, 1978; Choi, *et al.*, U.S. Patent No. 4,093,709, June 6,
1978; Schmitt, U.S. Patent No. 4,122,158, October 24, 1978; Choi,
et al., U.S. Patent No. 4,131,648, December 26, 1978; Choi, *et al.*,
30 U.S. Patent No. 4,138,344, February 6, 1979; Schmitt, U.S. Patent
No. 4,155,992, May 22, 1979; Choi, *et al.*, U.S. Patent No. 4,180,646,
December 25, 1979; Capozza, U.S. Patent No. 4,322,323, March 30,
1982; and Schmitt, U.S. Patent No. 4,346,709, August 31, 1982. The
disclosures in these patents are incorporated herein by reference.
35 Other bioerodible polymers which are of interest in this
invention are poly(lacticacid), poly(glycolic acid) and copolymers of

lactic acid and glycolic acid. Published literature relevant to
these polymers are Schmitt, et al., U.S. patent No. 3,991,766, issued
November 16, 1976; Yoles, S., et al., *Polymer News* 1(4/5):9-15
(1971); Kulkarni, R.K., et al., *J. Biomed. Mater. Res.* 5:169-181
5   (1971); and Wise, D.L., *Acta Pharm. Suecica* 13(suppl.):34 (1976).

       In these formulations in general, the drug is originally
dispersed in and held immobile by the polymeric matrix, and the
release of the drug from the matrix occurs gradually over a period of
time. This sustained release is achieved by one or a combination of
10   mechanisms, including diffusion of the drug through molecular
interstices in the polymer, diffusion of the drug through pores in
the polymer (if a pore-forming ingredient has been used in the
formation of the polymer), and degradation of the polymer itself.
The release rate may be controlled to a certain degree by varying
15   certain system parameters, such as the size and shape of the polymer
systems, the choice of polymer used to form the matrix, the molecular
weight and density of the polymer, the ratio of drug to polymer, the
pore structure of the matrix, the inclusion of additional components
such as erosion rate modifiers in the matrix, and the choice of
20   carrier vehicle where one is used.

       Degradation of the polymer is potentially the greatest
contributing factor to the release of the drug, since degradation
reduces and ultimately removes the diffusion barriers which retard
the passage of the drug through the matrix. Also, there are certain
25   drugs which are released from the matrix primarily by erosion or
degradation of the polymer and not by diffusion. Theoretically,
therefore, the release rate may be regulated either up or down by
increasing or decreasing the polymer degradation rate. Attempts to
do this in the prior art have involved the inclusion of erosion rate
30   modifiers as additives mixed in with the polymers, the modifiers
selected either to promote or to inhibit the degradation reaction.
Disclosures of erosion rate modifiers and their use appear in
Schmitt, U.S. Patent No. 4,346,709, August 31, 1982, which discloses
metals, metal oxides, metal oxide salts, metal hydroxides, amines,
35   organic and inorganic acids, and monobasic and polybasic acids, and
Capozza, U.S. Patent No. 4,322,323, March 30, 1982, which discloses
anionic, cationic and nonionic surfactants.

Modifiers known to the prior art are not always a satisfactory solution, however, since under certain circumstances the modifiers tend to diffuse out of the polymer into the surrounding medium. This causes a sharp drop in the effectiveness of the

5 modifier, and the resulting curve of the release rate of the drug *vs.* time changes in slope. This is particularly the case with highly water-soluble modifiers. When such a water-soluble modifier is a degradation inhibitor, for example, the desired slow release rate lasts only through the initial stages of the release period and·is

10 followed by release at a rate which is faster than desired. Conversely, when such a modifier is a degradation promoter, the desired fast release lasts only initially, leaving a significant quantity of the drug to be released from the polymer matrix at too slow a rate. The loss of effectiveness may be compensated for by

15 using a particularly strong modifier which will continue to work at low concentrations. In systems where the modifier is an acid or base, for example, a strong modifier will be one with a low pK_a or pK_b, respectively. High strength modifiers, however, can compromise the stability of acid- or base-sensitive drugs in the polymer system

20 and, depending on the modifier, raise physiological risks and toxicity questions by releasing free quantities of modifier when administered to a patient.

Additionally, prior art modifiers are often not satisfactory due to the fact that they have been incorporated into the polymer in

25 such a way that they are not mixed with the polymer on a molecular level but are present in a separate phase, which is dispersed on a supra-molecular level through the polymer matrix. This leads to a loss of efficiency and to the use of higher strength modifiers. Also, the high strength acid or base modifier, being in a separate

30 phase from the polymer, is available to come into contact with and adversely affect drugs or other agents present in the polymer matrix which are sensitive to the modifier.

The present invention addresses these and other disadvantages and shortcomings of these and other methods of

35 regulating the biodegradation rate of polymer matrices.

SUMMARY OF THE INVENTION

It has now been discovered that the biodegradation rate
of bioerodible polymers can be regulated in an unusually efficient
manner by the use of erosion rate modifiers whose solubility in the
polymer is high relative to their solubility in an aqueous medium.
Modifiers in accordance with this invention reside in the matrix as a
solute in the solid or semi-solid polymer, on a molecular level,
rather than as a separate solid or liquid phase, and have a greater
tendency to remain in solution in the polymer than to dissolve in,
and diffuse through, the generally aqueous environment in which the
polymer is placed for use.

By virtue of this tendency, the modifiers offer several
advantages over modifiers of the prior art. First, the modifiers may
be selected from milder compounds, for example, such as weaker acids
and bases and usually less toxic compounds. This lowers the risk of
harm to the physiological systems to which the formulation is being
administered, and the risk of undesired chemical attack by the
modifiers to the polymer or to the drug which is retained by the
polymer for controlled release. Second, the modifiers of the
invention permit one to achieve stronger modifications in the
degradation rate, since they are in closer proximity to the polymer
and remain so during the life of the polymer. Third, the modifiers
permit one to achieve substantial and effective results with a lower
loading of modifier, which improves the economy of materials used,
and requires less interference with and variation of the chemical
composition of the formulation.

The invention is of particular interest in its
application to bioerodible polymers whose biodegradation rate is
regulated by acids or bases. The biodegradation reaction may occur
by any of a variety of mechanisms. Hydrolysis is one of the most
prominent of these mechanisms, occurring either alone or in
conjunction with enzyme action in a biological environment.
Depending on the type of polymer involved, the hydrolysis may be
accelerated or inhibited by acids, bases, or both.

Further features, embodiments, applications and
advantages of the invention will become apparent from the description
which follows.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1a, 1b and 1c illustrate graphically the rate of erosion
of a polymer/weak base single phase composition of the present
invention (FIG. 1a) in comparison with a polymer/weak base two-phase
composition (FIG. 1b) and the polymer alone (FIG. 1c).

FIGS. 2a and 2b illustrate graphically the rate of erosion of a
polymer/weak base single phase composition of the present invention
(FIG. 2a) and of a polymer/strong base two-phase composition (FIG.
2b).

DETAILED DESCRIPTION OF THE INVENTION
AND PREFERRED EMBODIMENTS

Erosion rate modifiers in accordance with this invention
are selected in accordance with the bioerodible polymer with which
they are intended for use. The selected modifiers are those which
form a solution with the polymer, and are used in amounts which
permit the entire amount of modifier to be dissolved in the polymer.
The modifier and polymer thus form a solid or semi-solid solution,
thereby forming a single phase, with molecules of the modifier
dispersed substantially uniformly and randomly throughout the
continuum of the polymer, as opposed to a two-phase solid in which
granules or globules of one are dispersed through, or suspended in,
the other.

It is not necessary that the modifier be soluble in the
polymer in all proportions. The upper solubility limit or saturation
point may indeed vary widely and is not critical. In most
applications, however, combinations in which the upper solubility
limit of the modifier in the polymer is at least about 1.0% by weight
will provide the best results. Preferred combinations are those in
which the upper solubility limit is at least about 3.0% by weight,
and most preferred are those in which the upper solubility limit is
at least about 6.0% by weight.

Conversely, the solubility of the modifier in water is
substantially lower than in the polymer. In preferred systems, the
modifier is substantially insoluble in water. By "substantially
insoluble in water", as used herein, is meant that the upper
solubility limit in water is at most about 0.5% by weight, and in
particularly preferred systems, it is at most about 0.1% by weight.

For applications of the invention in which the polymer
retains a drug or other beneficial agent for slow release, preferred
erosion rate modifiers are those which have a significantly lower
solubility in the drug than in the polymer. Preferred systems here
5   as well are those in which the upper solubility limit of the modifier
in the drug is at most about 0.5% by weight, and in particularly
preferred systems, at most about 0.1% by weight.

The selection of appropriate modifiers for any given
polymer, in terms of the solubility characteristics, is achieved by
10   routine and conventional methods. As is well known among those
skilled in physical chemistry and the chemistry of solutions, the
solubility of one species in another can be predicted without
experiment from a knowledge of the solubility parameters of the two
species. Published data on solubility parameters exists for a wide
15   range of compounds, and further data can be readily determined by
known methods. It is known that the closer the solubility parameters
of two substances are to each other, the greater the mutual
solubility. Determinations of appropriate modifiers for any given
polymer are then a direct consequence of the knowledge of their
20   solubility parameters.

Certain erosion rate modifiers may also serve as drugs or
other beneficial agents in themselves in the same or similar types of
sustained release delivery systems. The concentrations in which they
are present when used as erosion rate modifiers in accordance with
25   this invention, however, are in general considerably lower than those
in which they are present when used as drugs. One surprising aspect
of the invention, in fact, is that these agents have utility in the
polymer matrix at concentrations so much lower than those in which
they have been used as drugs. With this in mind, however, the
30   concentration used for purposes of erosion rate modification is not
critical and may vary widely. In most cases, best results will be
achieved at concentrations ranging from about 0.5% to about 15% by
weight, based on the polymer/modifier combination. Preferred
concentrations are from about 1% to about 10% by weight.

35   The solid or semi-solid solution of the erosion rate
modifier in the polymer may be formed by any conventional method. In
general, the most efficient methods involve combining the modifier

and polymer in liquid form, mixing thoroughly to achieve homogeneity, and then solidifying, preferably while forming the solidified solution into the desired ultimate shape. The components may be placed in liquid form by melting or by dissolving in solvents, then rendered solid at the appropriate stage by cooling or by solvent removal, as appropriate.

In certain cases, a pore-forming excipient is used during the formation of the polymer to form the polymer into a porous structure. In such cases, the excipient will generally be included in the liquid mixture as well. Pore-forming excipients and their use in forming porous polymer structures are well known in the art. When a pore-forming excipient of this nature is used, the erosion rate modifier is preferably one which has a greater solubility in the polymer than in the pore-forming excipient.

As indicated above, the invention permits the use of modifiers of moderate strength, since it extracts greater benefits from any given amount of modifier. In cases where the modifier is an acid or base, weak acids or bases may be used. In preferred embodiments, the acid or base will be one having a pK of at least about 2.0. For modifiers which are bases, in preferred embodiments the pK_b ranges from about 4.0 to about 10.0. Likewise, for modifiers which are acids, the pK_a in preferred embodiments ranges from about 4.0 to about 10.0.

Bioerodible polymers to which this invention is applicable vary widely. Certain classes of bioerodible polymers are preferred, however. One such class is that of the bioerodible poly(orthoester)s and poly(orthocarbonate)s referred to above. A particular subclass of these polymers is represented by Formula I below:

$$\left[\begin{array}{c} O \diagdown \diagup O - R^1 \\ C \\ (O)_a \diagup \diagdown O \\ R^2 \qquad R^3 \end{array}\right]_n \qquad (I)$$

·8
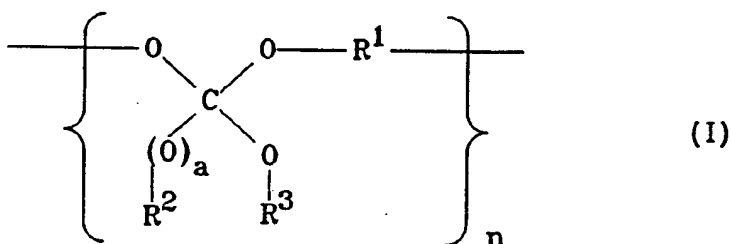
In the class defined by this formula:

The substituent R^1 is a divalent aliphatic or alicyclic
radical.

The substituents R^2 and R^3 either: (a) are both
monovalent radicals, not connected other than
through the linkage shown in the formula, and are
the same or different, or (b) together form a
single divalent radical, thereby forming a
heterocyclic ring with the two lower O atoms and
the C atom shown in the formula. Whether
monovalent or divalent, $i.e.$, whether taken
individually or combined, the two groups are either
aliphatic, alicyclic or aromatic radicals, or
radicals which are combinations of these types, or
radicals of these types which further contain
carbonyl or carbonyloxy groups.

As indicated above, the index "a" is zero or 1. When "a"
is zero, the polymer is a poly(orthoester), and
when "a" is 1, the polymer is a
poly(orthocarbonate).

Finally, the index "n" is a positive integer in excess of
3, and usually in excess of 10, indicating the
length of the polymer chain.

Various subclasses of ethers within the scope of
Formula I are preferred. For example, preferred groups for R^2 and
R^3, whether monovalent or divalent, are aliphatic, alicyclic or
aromatic radicals, or radicals which are combinations of two or all
three of these types. In a further preferred subclass, R^2 and R^3,
whether monovalent or divalent, are aliphatic or alicyclic. In a
still further preferred subclass, R^2 and R^3 when monovalent are
aliphatic or alicyclic and when divalent form an aliphatic group,
preferably saturated, and most preferably linear. As for R^1,
preferred groups are divalent aliphatic and alicyclic groups, the
aliphatic groups being preferably alkyl groups.

In further ways of characterizing the preferred
subclasses, R^1 is preferably 2 to 12 carbon atoms, and most
preferably 4 to 10 carbon atoms. Likewise, monovalent options for R^2

and R^3 are preferably 2 to 12 carbon atoms each, whereas divalent options are preferably 2 to 12 carbon atoms, more preferably 2 to 6 carbon atoms, and most preferably 3 to 4 carbon atoms.

The index "n" may be characterized by its value as it is above, or it may be characterized in terms of the molecular weight of the resulting polymer. In terms of molecular weight, "n" is preferably of a value which would provide the polymer with a molecular weight of at least about 1,000, and most preferably within a range of from about 1,000 to about 100,000.

Formula II below represents one preferred subclass of poly(orthoester)s:

(II)
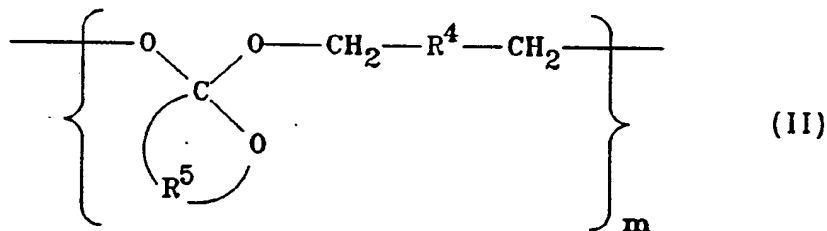
In this subclass, R^4 is either divalent cyclohexyl or divalent C_1-C_{10} alkyl, and R^5 is either $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_6-$. The index "m" is the counterpart to the index "n" in Formula I above, and has the same meaning and preferred ranges.

A still further subclass of poly(orthoester)s is that shown in Formula III:

(III)
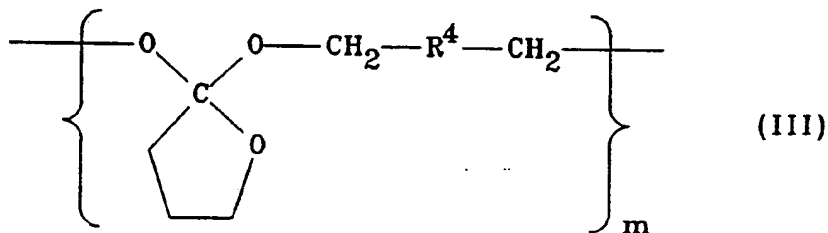
In this subclass, R^4 is either divalent cyclohexyl or divalent C_3-C_7
alkyl. Here again, the index "m" has the same meaning and range as
"n" described earlier.

Two particularly preferred poly(orthoester)s, which fall
under Formula III above, are poly(2,2-dioxy-1,6-hexamethylene
tetrahydrofuran) and poly(2,2-dioxy-cis,trans-1,4-cyclohexane
dimethylene tetrahydrofuran), each of which polymer has a molecular
weight of from about 1,000 to about 100,000. A typical molecular
weight of these polymers is 27,000.

A further preferred class of bioerodible polymers is the
class consisting of polymers and copolymers of hydroxycarboxylic
acids. Examples of these are polymers of d-lactic acid, polymers of
l-lactic acid, polymers of d,l-lactic acid, polymers of glycolic
acid, polymers of methylethylglycolic acid, copolymers of lactic and
glycolic acids, copolymers of caprolactone and lactic acids, and
mixtures thereof. Within this class, copolymers of d,l-lactic and
glycolic acids, conveniently referred to as poly(lactic/glycolic
acid), are particularly preferred.

Still further bioerodible polymers for use in this
invention are poly-beta-hydroxybutyrate, poly-beta-hydroxyvalerate,
poly-beta-hydroxybutyrate-beta-hydroxyvalerate, polycaprolactams and
polyanhydrides.

Although a wide range of erosion rate modifiers can be
used, certain modifiers have been found to be particularly effective
in certain polymer systems. For systems in which the polymer is
poly(2,2-dioxy-cis,trans-1,4-cyclohexane dimethylene tetrahydrofuran,
for example, lowering of the hydrolytic degradation rate can be
achieved by the incorporation of a weak base which meets the
parameters of this invention, while acceleration of the hydrolytic
degradation rate can be achieved by the incorporation of a weak acid.
This is also true of systems in which the polymer is poly(2,2-dioxy-
1,6-hexamethylene tetrahydrofuran), as well as other
poly(orthoester)s and poly(orthocarbonate)s of similar or analogous
structure.

One example of a weak base which is soluble in the
poly(orthoester) and not in aqueous media is bupivacaine, otherwise
known as *dl*-1-butyl-2',6'-pipecoloxylidide. It should be noted that

bupivacaine is itself useful as a local anesthetic and may thereby
serve as a beneficial agent to be retained by the polymer for
sustained release. When used as a beneficial agent, however, the
loading of bupivacaine in the polymer (i.e., its proportion relative
to the polymer) is generally at a level well in excess of its
saturation level, leaving a substantial portion of the bupivacaine
undissolved in the polymer. This is in contrast to its use as a
degradation rate regulator, in which the loading is at or below the
saturation level.

        One example of a weak acid for use with the
poly(orthoester) is benzoic acid.

        For systems in which the polymer is a polymer of
d,l-lactic acid, a polymer of glycolic acid, a mixture of the two, or
a copolymer of d,l-lactic and glycolic acids, both a weak base and a
weak acid will have the effect of accelerating the rate of hydrolytic
degradation. Bupivacaine and benzoic acids are again examples of a
weak base and a weak acid which will have this effect.

        The compositions of the present invention may
additionally include, if desired, one or more diluents, surfactants,
buffers, vehicles, stabilizers, dyes, inert fillers, pigments and
other components of polymeric matrix systems as are known in the art.

        In certain cases, a hydrophilic pore-forming excipient is
used during the formation of the polymer to form the polymer into a
porous structure. Such excipients may be chosen from a wide range of
materials. Examples are alkali metal salts such as sodium chloride
and potassium chloride; monosaccharides, oligosaccharides and poly-
saccharides, notably sucrose, glucose, fructose and trehalose;
polyalcohols such as mannitol and sorbitol; and water-soluble
cellulosic polymers such as methyl cellulose and hydroxypropylmethyl-
cellulose.

        Other excipients are optionally included. One class of
such excipients are inert hydrophobic excipients that act to increase
drug delivery and improve reproducibility from certain polymers.
Examples of this type of excipient are calcium stearate, magnesium
stearate, aluminum stearate, calcium phosphate, myciyl cerotate,
β-carotene, zeaxanthin, cholestane, 3-hydroxycholestane, cholesterol,
5,6-cholestene, 3-hydroxy-5,6-cholestene, and 3-amino-5,6-cholestene.

As indicated above, the invention is of particular
interest in sustained-release drug delivery formulations in which the
drug is incorporated in the polymer matrix together with the erosion
rate modifier. Incorporation of the drug into the polymer/modifier
5   matrix may be achieved in any of the various ways described in the
prior art. A prominent example is to combine the drug with the
polymer and modifier in a liquid form to achieve the appropriate
weight ratio and consistency, and then to solidify the combined
polymer and drug while forming the combination into the desired size
10   and shape. The drug is typically present in the polymer in a
therapeutically effective amount, by which is meant an amount that is
necessary to effect a therapeutic result. In practice, the
particular amount will vary widely, depending on many factors, such
as the drug to be delivered, the therapeutic effect desired, the
15   chosen environment of use, the rate of delivery, the length of
treatment, and the like.

The term "drug" is used in this specification in a broad,
generic sense, to include any physiologically or pharmacologically
active substances that produce a localized or systemic effect or
20   effects in animals. Examples of drugs will be readily apparent to
those skilled in the art. Therapeutic agents or drugs with which the
polymers of the present invention are particularly useful are those
agents which are sensitive to acids or bases, such as, for example,
proteins and peptides.

25   In the practice of the present invention, the delivery
devices of the invention are placed in or on an aqueous environment
of use. The environments in which the devices may be used include
physiological environments within the body of a human or animal or
aqueous environments such as pools, tanks, reservoirs, and the like
30   serving recreational, industrial or residential purposes. The
devices may also be utilized in the biotechnology area, such as to
deliver nutrients or growth regulating compounds or other agents to
cell cultures, for example. In the presently preferred embodiments,
the environment of use is the body of an animal. Included in the
35   term "animal" are humans, primates, mammals, domesticated or semi-
domesticated animals (such as household, pet, and farm animals),
laboratory animals (such as mice, rats and guinea pigs), birds,

reptiles, fish, zoo animals, and the like. The devices may be placed
on or in wounds, spread as a thin film, or injected as microparticles
or placed subcutaneously or interperitoneally as an implant into the
body, for example.

The delivery devices of the present invention can take a
variety of shapes and sizes, such as sheets, films, rods, fibers,
monofilaments, pellets, spheres and spheroids, particles and
microparticles, powders, tubes, discs, rings, and the like, depending
on the use to which they will be applied. The devices can be sized,
shaped and adapted for implantation, insertion, placement, depositing
or spreading on the body, in the body, or in cavities and passageways
of the body of an animal. The devices can be manufactured by
standard techniques known to the art.

The following examples are offered for purposes of
illustration, and are intended neither to limit nore to define the
invention in any manner.

EXAMPLE 1

A comparison was conducted, as follows, of the
degradation rate of a polymer/weak base matrix of the present
invention with that of the polymer without a base additive and of the
polymer together with the weak base where the base is in a separate
phase.

The polymer/base matrix of the invention was prepared by
mixing together, at 120°C, bupivacaine base (5%) and the
poly(orthoester) of Formula IV (above), having a molecular weight of
about 30,000, until the two components were well blended. The
resulting single-phase blend was melt-pressed into a sheet of 0.25 mm
thickness. The sheet was then cut into 1 cm x 1 cm squares. All the
processing was carried out under dry nitrogen gas. The squares were
packaged in double foil pouches and irradiated, receiving a dose of
2.5 Mrad of beta radiation.

A polymer/base matrix according to the prior art was
prepared by mixing together, at 60°C, bupivacaine base (5%) and the
poly(orthoester) of Formula IV, having a molecular weight of about
30,000, until the two components were well mixed. The resulting two-

phase mixture was then formed into squares and irradiated following
the procedures described above.

The poly(orthoester) alone was heated to 60°C and formed
into squares and irradiated following the above procedures.

5   A degradation rate experiment was conducted on samples
from each of the above systems by placing the irradiated systems in 5
mL of pH 7 0.01 M sodium phosphate buffer (which also contained 0.9%
of NaCl and 0.02% NaN$_3$). Samples of the release rate media were
taken each day and tested for presence of cyclohexanedimethanol. The

10   release of cyclohexanedimethanol (diol) is an indication of polymer
erosion. The resulting diol release for each system is presented in
FIG. la (polymer/bupivacaine single-phase blend), **FIG. lb**
(polymer/bupivacaine two-phase mixture), and **FIG. lc** (polymer alone).
The systems having the bupivacaine and polymer together in a single-

15   phase showed a markedly slower rate of erosion than either the
polymer/bupivacaine two-phase mixture or the polymer alone.

EXAMPLE 2

A comparison was made as follows of the degradation rate
of a polymer/weak organic base matrix of the present invention with

20   that of a polymer/strong inorganic base matrix of the prior art.

Inorganic bases generally can achieve higher pH values
than organic bases, and thus are considered to be stronger bases.
For example, a saturated solution of dibasic potassium phosphate has
a pH of 11 whereas a saturated solution of bupivacaine base has a pH

25   below 9. This is a 100+ fold difference in concentration of hydroxyl
ions.

A composition of poly(orthoester) and bupivacaine base,
formed as a single phase, was prepared by mixing together, at a
temperature of 120°C, bupivacaine base (8%) and the poly(orthoester)

30   of Formula IV (above; 92%), having a molecular weight of about
30,000. Part of this single-phase blend (650 mg) was then mixed at
60°C with lysozyme (a protein; 50 mg), trehalose (150 mg), pH 7
potassium phosphate buffer (25 mg of dibasic potassium phosphate and
25 mg of potassium dihydrogenphosphate), and cholesterol (100 mg).

35   The lysozyme and trehalose had been previously co-lyophilized. All
the ingredients, except the polymer/bupivacaine mix, were micronized

to 5 microns and dried to a water content of less than 0.1% prior to mixing. The resulting mixture was melt-pressed into a sheet of 0.25 mm thickness. The sheet was then cut into 1 cm x 1 cm squares. All the processing was carried out under dry nitrogen gas. The squares were packaged in double foil pouches and irradiated, receiving a dose of 2.5 Mrad of beta radiation.

A composition of poly(orthoester) and dibasic potassium hydrogenphosphate, as a mixture together with lysozyme, was prepared by mixing together lysozyme (100 mg), dibasic potassium phosphate (50 mg), cholesterol (150 mg) and the poly(orthoester) of Formula IV (700 mg) in a mixer heated at 60°C for 10 minutes. The lysozyme, dibasic potassium phosphate and cholesterol were previously micronized to a particle size of 5 microns and dried to a water content of less than 0.1%. The resulting polymer/base/lysozyme mixture was then formed into squares and irradiated following the procedures described above.

A degradation rate experiment was conducted on samples from each of the above systems by placing the irradiated systems in 5 mL (polymer/bupivacaine single-phase system) or 10 mL (polymer/dibasic potassium phosphate two-phase system) of pH 7 0.01 M sodium phosphate buffer (which also contained 0.9% of NaCl and 0.02 M NaN$_3$). Samples of the release rate media were taken each day and tested for presence of cyclohexanedimethanol. The release of cyclohexanedimethanol (diol) is an indication of polymer erosion. The resulting diol release for each system is presented in **FIGS. 2a** (polymer/bupivacaine single-phase system) and **2b** (polymer/dibasic potassium phosphate two-phase system). The erosion of the systems containing bupivacaine was of approximately the same degree of slowness as that of the system with dibasic potassium phosphate, even though bupivacaine is a much weaker base than dibasic potasisum phosphate.

EXAMPLE 3

PLGA [poly(lactic-glycolic acid), 50:50 lactic:glycolic acids, Resomer® RG 503, Boehringer Ingelheim] was mixed with 10% (w/w) of either benzoic acid or pyruvic acid. The mixing was done in a 1.5 cc mechanical polymer mixer, in both cases at temperatures

above the melting point of the acid to give single-phase blends. The
mixing temperature was initially around 140°C, and was subsequently
lowered as the mixed-in acids plasticized the polymer. In both
cases, clear mixtures were obtained.

5   The intention of mixing acids in PLGA is to increase the
degradation rate of the polymer. The degradation rates of the two
polymer blends and of neat PLGA were compared. Benzoic acid, having
a very low solubility in water at 37°C, was retained well in the PLGA
and was an effective degradation rate enhancer. After 4 weeks in a
10   phosphate buffered physiological saline solution at 37°C, neat PLGA
was about 60% degraded, while the PLGA with benzoic acid was more
than 90% gone. In contrast, pyruvic acid, being highly water
soluble, was rapidly lost to the release medium, and accelerated the
degradation much less efficiently. The polymer with the pyruvic acid
15   initially degraded more rapidly than the neat PLGA, but over time its
degradation rate accelerated less than that of the neat PLGA, and
after 4 weeks about 65% of the PLGA with pyruvic acid was degraded.


           The foregoing is offered primarily for purposes of
illustration. It will be readily apparent to those skilled in the
20   art that the materials, proportions, operating conditions, and other
parameters of the systems and methods described herein may be further
modified or substituted in various ways without departing from the
spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A method for treating a polymer which is non-
water-soluble but bioerodible to modify the rate of bioerosion of
said polymer, said method comprising incorporating into said polymer
an erosion rate modifier selected from an acid or a base which is
soluble in said polymer and substantially insoluble in water and has
a pK of at least 2.0, at a concentration at or below the upper
solubility limit of said erosion rate modifier in said polymer, said
erosion rate modifier and said polymer forming a single homogeneous
phase.

2. A method in accordance with claim 1 in which said
erosion rate modifier is a base having a pK_b of from about 4.0 to
about 10.0.

3. A method in accordance with claim 1 in which said
erosion rate modifier is an acid having a pK_a of from about 4.0 to
about 10.0.

4. A method in accordance with claim 1 in which said
polymer is a member selected from the group consisting of
poly(orthoester)s, poly(orthocarbonate)s, polymers of d,1-lactic
acid, polymers of glycolic acid, copolymers of d,1-lactic and
glycolic acids, and mixtures thereof.

5. A method for treating a bioerodible polymer
selected from the group consisting of poly(orthoesters) and
poly(orthocarbonates) to lower the rate of bioerosion thereof, said
method comprising incorporating into said bioerodible polymer a base
which is soluble in said bioerodible polymer and substantially
insoluble in water and has a pK_b of at least about 2.0, at a
concentration at or below the upper solubility limit of said base in
said bioerodible polymer, said base and said polymer forming a single
homogeneous phase.

6. A method in accordance with claim 5 in which said
base is bupivacaine base.

7. A method in accordance with claim 5 in which said
bioerodible polymer is a polymer having the formula
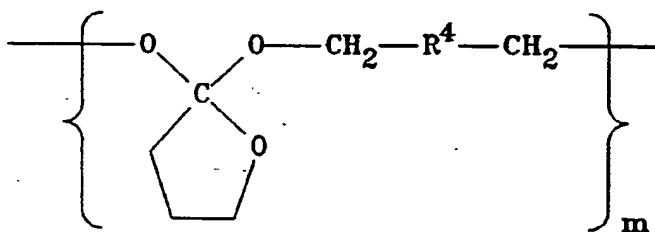
in which:

R^4 is a member selected from the group consisting of
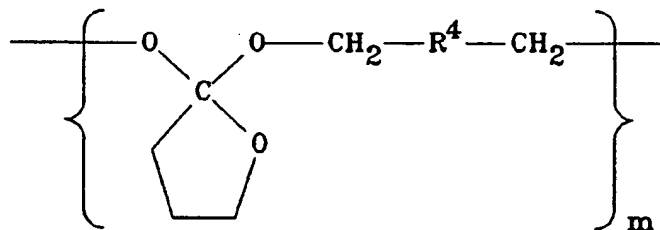divalent cyclohexyl and divalent C$_3$-C$_7$ alkyl; and
m is a positive integer high enough such that said ortho
polymer has a molecular weight of from about 1,000
to about 100,000; and
said base is bupivacaine base.

8. A method for treating a bioerodible polymer
selected from the group consisting of poly(orthoesters) and
poly(orthocarbonates) to accelerate the rate of bioerosion thereof,
said method comprising incorporating into said bioerodible polymer an
acid which is soluble in said bioerodible polymer and substantially
insoluble in water and has a pK$_a$ of at least about 2.0, at a
concentration at or below the upper solubility limit of said acid in
said bioerodible polymer, said acid and said polymer forming a single
homogeneous phase.

9. A method in accordance with claim 8 in which said
acid is benzoic acid.

10.   A method in accordance with claim 8 in which said
bioerodible polymer is a polymer having the formula

$$-\left\{ \begin{array}{c} O \\ \diagdown C \diagup \\ | \\ O \end{array} \right\}_m -O-CH_2-R^4-CH_2-$$

in which:

5   R^4 is a member selected from the group consisting of
          divalent cyclohexyl and divalent C_3-C_7 alkyl; and
      m is a positive integer high enough such that said ortho
          polymer has a molecular weight of from about 1,000
          to about 100,000; and
10 said acid is benzoic acid.

11.   A method for treating a bioerodible polymer
selected from the group consisting of polymers of d,1-lactic acid,
polymers of glycolic acid, copolymers of d,1-lactic and glycolic
acids, and mixtures thereof, to accelerate the rate of bioerosion
15 thereof, said method comprising incorporating into said bioerodible
polymer an additive selected from the group consisting of acids and
bases which are soluble in said bioerodible polymer and substantially
insoluble in water and have a pK of at least about 2.0, at a
concentration at or below the upper solubility limit of said additive
20 in said bioerodible polymer, said additive and said polymer forming a
single homogeneous phase.

12.   A method in accordance with claim 11 in which
said additive is a member selected from the group consisting of
bupivacaine base and benzoic acid.

25   13.   A method in accordance with claim 11 in which
said bioerodible polymer is a copolymer of d,1-lactic and glycolic

acids, and said additive is a member selected from the group
consisting of bupivacaine base and benzoic acid.

       14.   A bioerodible polymer matrix system which
comprises a bioerodible polymer and an erosion rate modifier selected
5   from an acid or a base which is soluble in said polymer and
substantially insoluble in water and has a pK of at least 2.0, said
erosion rate modifier being dissolved in said bioerodible polymer at
a concentration at or below the upper solublity limit of said erosion
rate modifier in said bioerodible polymer, said erosion rate modifier
10 and said polymer forming a single homogeneous phase.

       15.   A bioerodible polymer matrix system in accordance
with claim 14 in which said erosion rate modifier is a base having a
pK_b of from about 4.0 to about 10.0.

       16.   A bioerodible polymer matrix system in accordance
15 with claim 14 in which said erosion rate modifier is an acid having a
pK_a of from about 4.0 to about 10.0.

       17.   A bioerodible polymer matrix system in accordance
with claim 14 wherein said polymer is a member selected from the
group consisting of poly(orthoester)s and poly(orthocarbonate)s and
20 said erosion rate modifier is bupivacaine base.

       18.   A bioerodible polymer matrix system in accordance
with claim 14 wherein said polymer is a member selected from the
group consisting of polymers of d,l-lactic acid, polymers of glycolic
acid, copolymers of d,l-lactic and glycolic acids, and mixtures
25 thereof and said erosion rate modifier is selected from the group
consisting of bupivacaine base and benzoic acid.

       19.   A delivery device for the controlled
administration of a beneficial agent to an environment of use,
wherein the device comprises:
30   (a)   a shaped matrix sized and adapted for
                administering a drug to an animal, said matrix comprising

a bioerodible polymer and an erosion rate modifier
selected from an acid or a base which is soluble in said
polymer and substantially insoluble in water and has a pK
of at least 2.0, said erosion rate modifier being
5   dissolved in said bioerodible polymer at a concentration
at or below the upper solublity limit of said erosion
rate modifier in said bioerodible polymer, said erosion
rate modifier and said polymer forming a single
homogeneous phase; and
10   (b) the drug to be delivered, dispersed in said
matrix in a therapeutically effective amount.

        20. A delivery device in accordance with claim 19 in
which said erosion rate modifier is a base having a pK_b of from about
4.0 to about 10.0.

15   21. A delivery device in accordance with claim 19 in
which said erosion rate modifier is an acid having a pK_a of from
about 4.0 to about 10.0.

        22. A delivery device in accordance with claim 19
wherein said polymer is a member selected from the group consisting
20 of poly(orthoester)s and poly(orthocarbonate)s and said erosion rate
modifier is bupivacaine base.

        23. A delivery device in accordance with claim 19
wherein said polymer is a member selected from the group consisting
of polymers of d,1-lactic acid, polymers of glycolic acid, copolymers
25 of d,1-lactic and glycolic acids, and mixtures thereof and said
erosion rate modifier is selected from the group consisting of
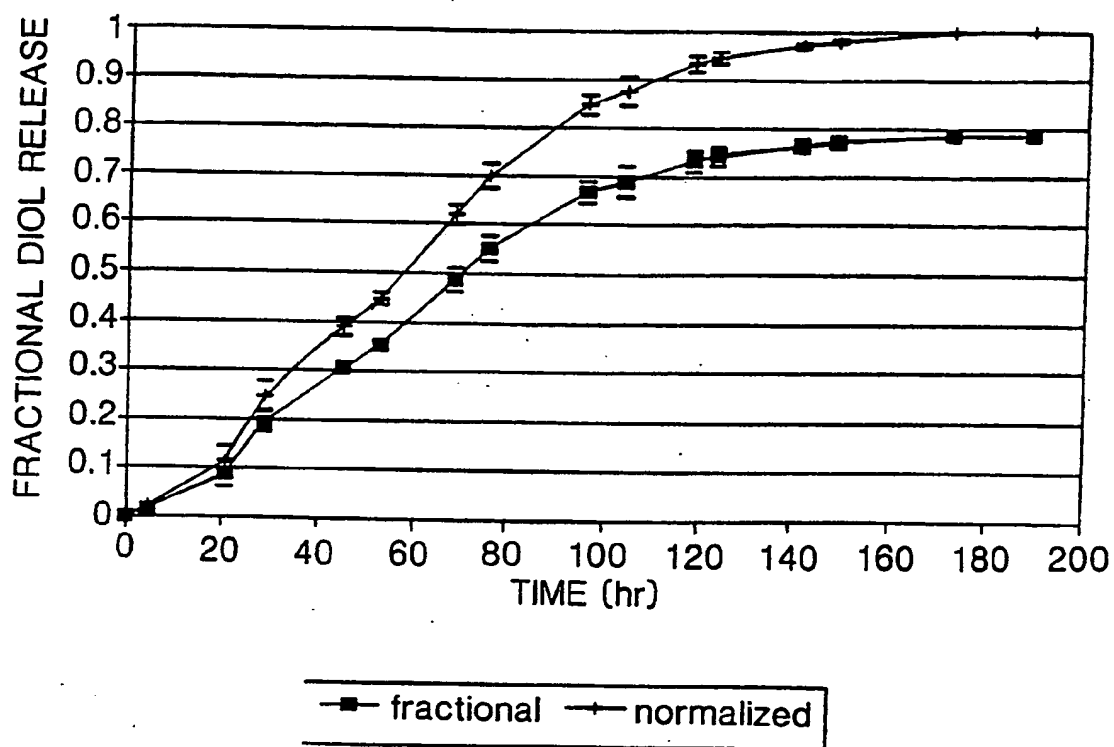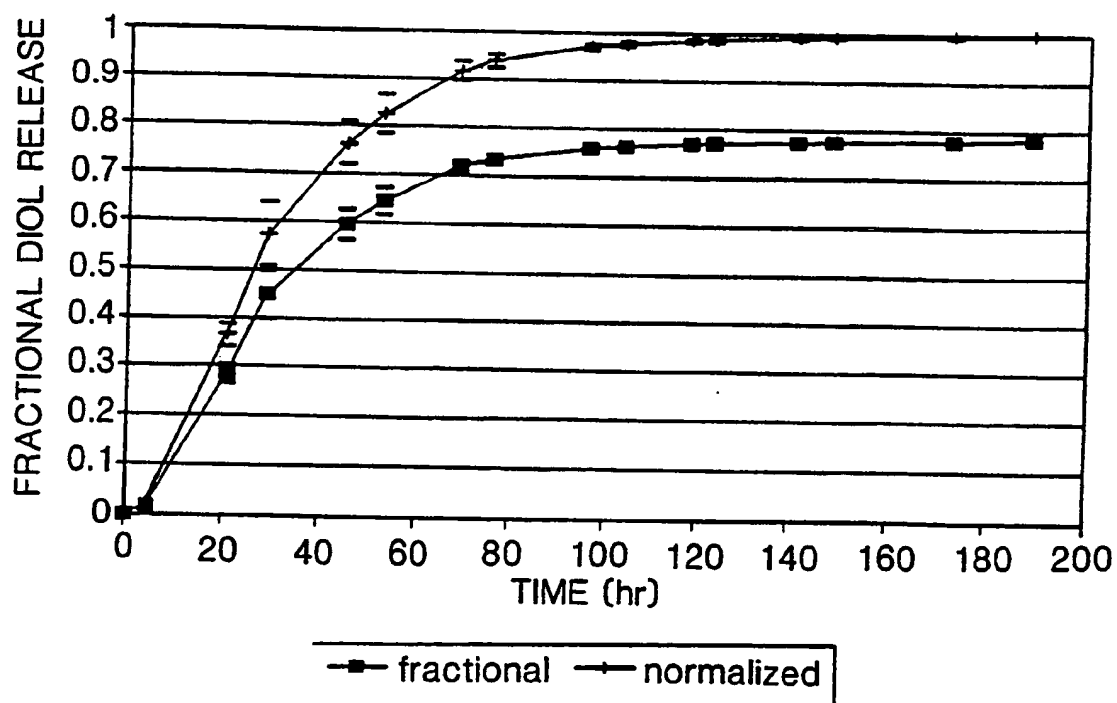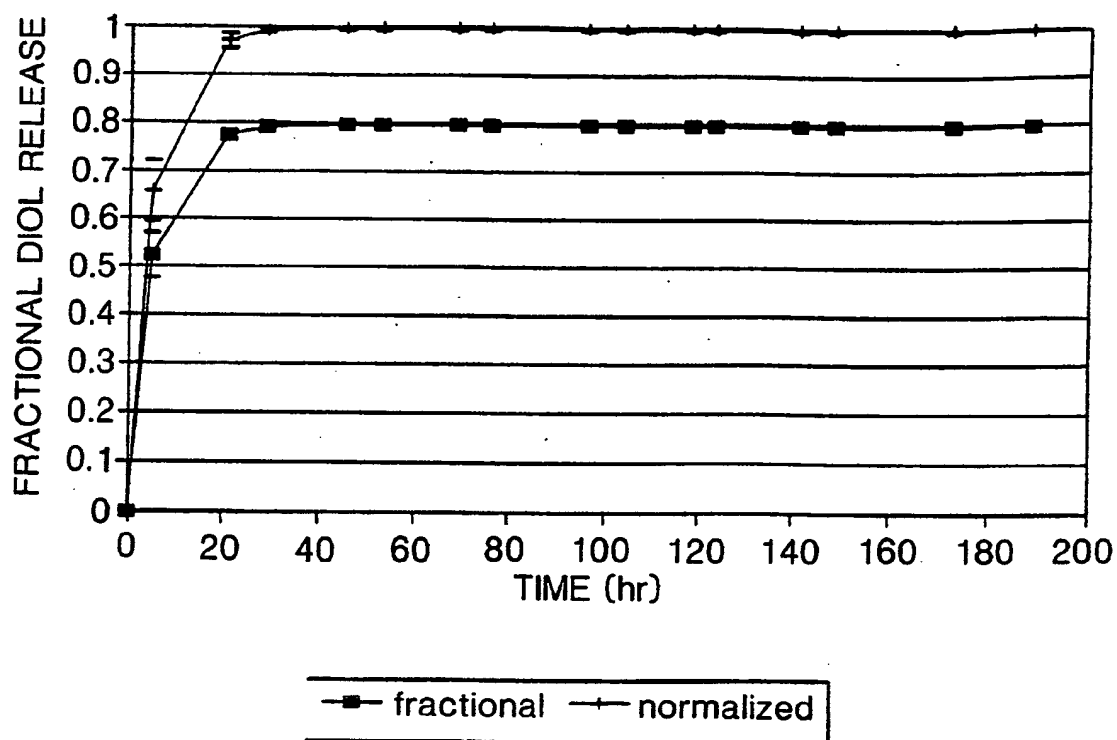bupivacaine base and benzoic acid.

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FIG. 1a

- fractional - normalized

FIG. 1b

- fractional - normalized

FIG.1c

Legend: fractional, normalized

(Y-axis: FRACTIONAL DIOL RELEASE, 0 to 1; X-axis: TIME (hr), 0 to 200)

FIG.2a

FIG.2b

I. CLASSIFICATION OF SUBJECT MATTER   (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C08K5/00;   A61K9/22

II. FIELDS SEARCHED

Minimum Documentation Searched[7]	
Classification System	Classification Symbols
Int.Cl. 5	C08K ; A61K ; C08L

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[°]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	US,A,4 346 709 (SCHMITT) 31 August 1982 cited in the application see claims 1,6,12,13; examples 23,25 ---	1
P,X	WO,A,9 213 567 (NOVA PHARMACEUTICAL CORPORATION) 20 August 1992 see claim 1; examples 2,3 ---	1,5,6
X	JOURNAL OF CONTROLLED RELEASE vol. 15, no. 1, February 1990, AMSTERDAM NL pages 55 - 63 SHIH, LUCAS, ZENTNER 'Acid catalyzed poly(ortho ester matrices for intermediate term drug delivery' see page 61, right column, line 1 - line 3 ---	1

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22 JUNE 1993	1 9. 07. 93

International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Dieter Schüler

III. DOCUMENTS CONSIDERED TO BE RELEVANT   (CONTINUED FROM THE SECOND SHEET)

Category°	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	PHARMAZIE vol. 47, no. 6, 1992, BERLIN DD pages 436 - 439 THOMA, SCHLÜTERMANN 'Beziehungen zwischen Herstellungsparametern und pharmazeutisch-technologischen Anforderungen an biodegradierbare Mikropartikel' see figure 5 —————	1

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.   22/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4346709	31-08-82	EP-A,B 0052916	02-06-82
WO-A-9213567	20-08-92	AU-A- 1643292	07-09-92

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82